UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/883,848	06/18/2001	Leona E. Ling	CIBT-P01-119	9957

28120 7590 03/03/2008

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
03/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/883,848	LING ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,26 and 37-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 26 and 37-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/03/2007 and 12/10/2007* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 12/03/2007 in response to the previous Non-Final Office Action (10/20/2004) is acknowledged and has been entered.

Claims 1-2, 26 and 37-74 are currently pending and under consideration.

Information Disclosure Statement

The Information Disclosure Statements filed on 12/03/2007 and 12/10/2007 are acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS's are attached hereto.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 26, 37-38 and 42-58 remain rejected and new claims 59-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baron et al. (WO 98/35020, 1998, *of record*) in view of Porter et al. (US 6,613,798, 2003, *of record*).

Baron et al. teach a method of treating a subject suffering from an ischemia in tissues containing mesodermally derived cells comprising administering a compound to the ischemic site so as to stimulate vascular growth, wherein the ischemia is myocardial ischemia and the compound is an agonist of a hedgehog-protein-receptor (page 5, lines 1-5 and page 53, lines 20-30). With regards to the compounds, the WO document teach that compounds of the invention include, but are not limited to, molecules which interact with membrane proteins which initiate signal transduction pathways such as smoothened, patched and gli which regulate hematopoiesis and vascular growth;

and include, but are not limited to, hedgehog proteins and synthetic agonists (page 17, line 26 to page 18, line 7).

Baron et al. do not explicitly teach that the synthetic agonist is a hedgehog agonist having the formula XII with a molecular weight of less than 750 amu. Nor does Baron et al. teach that the compound is administered systemically.

Porter et al teach small organic agonist that are capable of promoting proliferation in cells by modulating the hedgehog pathway, wherein the small organic agonists encompasses the claimed small organic compounds of formula XII, as well as the claimed substituents claimed in Claims 43-57 and molecular weight (column 6, formula I, column 19, lines 3-10 and Column 7, lines 5 to lines 65). With regards to the hedgehog pathway, the patent teaches that the small organic agonist can modulate the signal transduction pathway regulated by hedgehog, pathched (ptc), gli and/or smoothened (column 18, lines 40-43). Moreover, Porter et al. teach (column 54, lines 19-25) that the small organic agonist may be administered to a patient suffering from severe congestive heart failure (CHF) characterized by cardiac cachexia, as well as for promoting wound healing resulting from surgery, wherein the wound heals with less scarring (column 61, lines 8-27). With regards to the administration, the patent teaches that the agonist may be administered systemically at a dosage of 0.0001 to about 100 mg per kilogram (column 67, lines 1-8 and lines 46-59).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to use the specifically taught small organic agonists taught by Porter et al. in the method of treating a subject suffering from myocardial ischemia as taught by Baron et al.. One would have been motivated to do so because Porter et al. teach that the small organic agonist modulate the signal transduction pathway regulated by hedgehog, pathched (ptc), gli and/or smoothened (column 18, lines 40-43). Thus, one or ordinary skill in the art would have a reasonable expectation of success that by administering small organic hedgehog agonist as taught by Porter et al., one would achieve an treating a subject suffering from an myocardial ischemia.

Claims 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baron et al. (WO 98/35020, 1998, *of record*) in view of Porter et al. (US 6,613,798, 2003, *of record*), as applied above to claims 1-2, 26, 37-38 and 42-58 and new claims 59-74, and in further view of Igo et al. (US 5,681,278, 1997, *of record*).

Baron et al. in view of Porter et al. teach a method of treating a subject suffering from an ischemia in tissues containing mesodermally derived cells comprising systemically administering a compound to the ischemic site so as to stimulate vascular growth, wherein the ischemia is myocardial ischemia and the compound is an hedgehog agonist encompassed by the instantly claimed compounds of Formula XIII.

Baron et al. in view of Porter et al. do not explicitly teach that the agonist is administered by direct injection to ischemic myocardium, intrapericardial administration or by intracoronary catheter delivery.

Igo et al. teach method for treating blood vessels in a mammal, especially the coronary blood vessels (abstract). Specifically, the patent teaches that the blood vessels can be treated by administering an agent intracoronarally to reopen the thrombosed vessel and reduce the incidence of myocardial infarction or intrapericardial injection (column 3, lines 9-16 and column 6, lines 21-22). With regards to intrapericardial injection, Igo et al. teach that many agents have been injected into the pericardial space allowing for a site specific delivery of the agent which attains higher, longer lasting drug levels in the pericardial fluid with lower plasma concentrations and less systemic toxicity (column 6, lines 23-28).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the routes of administration of the hedgehog agonist as taught by Baron et al in view of Porter et al. for the treatment of a patient following myocardial infarction. One would have been motivated to do so because it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. Moreover, as taught by Igo et al., intrapericardial administration allows for a site specific delivery of the agent which attains higher, longer lasting drug levels in the pericardial fluid with lower plasma concentrations and less systemic toxicity. Thus, one or ordinary skill in the art would have a reasonable expectation of success that by optimizing the administration routes of the hedgehog agonist as taught by Baron et al. in view of Porter et al., one would achieve an method of selectively targeting the blood vessels of a patient following myocardial infarction.

In response to these rejections, Applicants assert that while the Examiner alleges that the induction of VEGF expression would flow naturally from following the suggestion of the prior

art, the Examiner has provided no evidence to support this statement and further, Applicants have provided references indicating that VEGF expression is not necessarily associated with angiogenesis, See, Belperio et al., 2000, J Leukocyte Biol 68: 1-8; Douglas and Nicolls, J Clinical Investigation, 2005, 115:1133-1136, cited in the previous response. Secondly, Applicants assert that the Examiners reliance on Ex Parte Obiaya as providing a legal basis for the rejection is misplaced, wherein the present case is distinguishable from Obiaya on, at least, three grounds. First, Applicants assert that the claims at issue in Obiaya were directed to an apparatus, which is in contrast to the present claims directed towards methods. Secondly, Applicants assert that the inherent feature that allegedly distinguished the claimed device in Obiaya from the prior art was based on the use of the apparatus and was not based on additional, patentable features incorporated into the apparatus itself as in the present case. Thirdly, Applicants assert that the issue in Obiaya was whether the patent applicant provided sufficient evidence of secondary considerations to rebut the prima facie case of obvious. In contrast, Applicants assert that the issue in the present case is whether the Examiner has satisfied the requirements for making a prima facie case of obviousness. For example, Applicants assert "do the cited references teach or suggest each and every limitation of the claimed invention?" As detailed above, Applicants submit that the Examiner has acknowledged that the cited references fail to teach a method for promoting VEGF expression. Thus, Applicants assert that the references fail to teach each and every limitation of the claimed invention, and the Examiner has, by his own admission, failed to establish a prima facie case of obviousness. Lastly, Applicants assert that although inherency is often relevant in the context of anticipation, it is rarely relevant to the assessment of obviousness. As such, Applicants assert that the Examiner's reliance on the alleged inherent features of the prior art to bridge the gap between the teachings of the prior art and the claimed invention is misplaced.

These arguments have been carefully considered, but are not found persuasive.

First, the Examiner acknowledges and does not dispute Applicants assertions that VEGF expression is not necessarily associated with angiogenesis. However, the Examiner maintains that the induction of VEGF expression would flow naturally from following the suggestion of the prior art. In the instant case, Applicants have not provided any evidence that the dosage of the small organic agonist taught by Porter et al. is not an effective amount to induce VEGF. As stated above,

Baron et al teach treating the same patient population, e.g., subjects with ischemic myocardial tissue, using agonists, such as synthetic agonist, of a hedgehog-protein receptor, while Porter et al. teach small organic agonists encompassed by the claimed small organic compounds of formula XII, as well as the claimed substituents claimed in Claims 43-57 and molecular weight which modulate the signal transduction pathway regulated by hedgehog, pathched (ptc), gli and/or smoothened and further, that the agonist may be administered systemically at a dosage of 0.0001 to about 100 mg per kilogram. Regarding Applicants assertions pertaining to Ex Parte Obiaya, the Examiner acknowledges and does not dispute Applicants assertions regarding Ex Parte Obiaya. However, the Examiner recognizes that while in Obiaya the claims were drawn to a product and the section relied upon by the Examiner pertains to secondary consideration, the fact patterns involved in Obiaya are similar to the methods claimed in the pending application. For example, in Obiaya the Appellant presented evidence to indicate that a shorter response time is obtained when a labyrinth heater is employed, this being an unexpected result. However, the Courts found that the references disclosing labyrinth heaters indicate that the advantage obtained by using such heater is that samples are maintained at a uniform temperature. The fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. Note In Re Best 195 USPQ 430 (CCPA 1977) and In Re Wilder 166 USPQ 545 (CCPA 1970). In the instant case, as described above, the prior art references teach treating the same patient population as claimed using the same hedgehog agonist as claimed; and further, a dosage for the hedgehog agonist as claimed. Hence, induction of VEGF expression would flow naturally from the teachings described above. In addition, while Applicants have found that VEGF expression is induced upon administration of the hedgehog agonist to a patient with ischemic mycocardial tissue, Applicants have not provided a patentable difference between the combination of the prior art. In particular, that the dosage of hedgehog agonist as disclosed by Porter would not induce VEGF expression. In the instant case, the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte

Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Regarding Applicants contention that the combination does not teach each and every limitation, the Examiner does not dispute that it was stated in the prior office action that the cited references fail to teach a method for promoting VEGF expression. However, the Examiner recognizes that this recitation has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Therefore, No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Primary Examiner
Art Unit 1642

/Brandon J Fetterolf, PhD/
Primary Examiner, Art Unit 1642